IMMUNITY IN TUBERCULOSIS: WITH SPECIAL REFERENCE TO RACIAL AND CLINICAL MANIFESTATIONS.[1]

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Nine years ago Professor Theobald Smith[2] delivered an address before this body on the subject of tuberculosis, with especial reference to the parasitic properties of the tubercle bacilli. He gave a most illuminating view of the bacillus from the biologist's point of view as well as a working theory of the reciprocal action of the tissues and parasite.

I refer to his hypothesis that the bacillus forms a protective envelope or capsule which permits it to retain vitality in a latent focus. He further explained the mechanism of infection and immunity, and presented the problem for clinical medicine as developed up to that time.

I fear that my selection for a similar task is inadequate; certainly I am deeply conscious of the responsibility and honor in offering the Harvey Society this effort to supplement that of our most distinguished American worker in tuberculosis.

It appeared to me better suited and more useful at the present time to treat the subject of immunity in its clinical aspect, and, while discussing some of the recent laboratory researches, to take also a broad survey of tuberculosis from the racial and epidemiological view-point. We may in this way discover a proper attitude toward the complex problem of prevention and treatment of tuberculosis, a matter fraught with frequent misunderstandings and wide differences of opinion. Only by this combination of experimental and clinical experience have we any claim to judicious decisions. Too often we encounter confusion and perplexity in the face of the frequent contradictions met with in tuberculosis from the clinical side. The deceptions and fallacies of laboratory experiments have also led us astray to the discouragement of many. It must be admitted to be a difficult field, yet not barren of encouraging results to the patient worker.

To begin the theme of immunity, one must at once discard the meaning of absolute protection usually conveyed by it and employ the expression "relative immunity," or, better, "heightened resistance." We know, so far as tuberculosis is concerned, that in man no absolute immunity has been observed, meaning by this, *effective resistance throughout life*. The actuality is quite otherwise;

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[1] Harvey Lecture, New York Academy of Medicine, January 16, 1915.
[2] Ibid., 1906, Jour. Amer. Med. Assoc., April 28, 1906.

yet many individuals unquestionably attain it in a practical sense in that no disease follows infection with tubercle bacilli.

From the pathologist's view-point few escape the formation of tubercles from the introduction of the bacilli. Even the nearly refractory animals, like the goat, cat, or dog, form primary foci. The immunity is thus not against infection but against its further spread. On the other hand, by the extensive observations of Harbitz,[3] Bartel,[4] and many others we know that living tubercle bacilli may lodge in the lymph glands for a considerable time without producing infection or tuberculous tissue. Doubtless many are disposed of before they have a chance to multiply. Nevertheless, given the proper conditions for multiplication and a bacillus of sufficient virulence or adaptability, it is perfectly conceivable that a single bacillus may suffice for infection. We must keep in mind the reciprocal relations between host and parasite, so well emphasized by Professor Smith, to understand why an infection may be balanced by the defenses and fail to make headway beyond the primary focus or port of entry.

Some of the conditions favorable to immunity are fairly defined; others elude our search or can only be stated in vague terms. Inoculated bacilli will at least act as irritant foreign bodies, unlike most bacteria, owing to their waxy substance; yet we can be certain that small numbers of bacilli, for example, or those of low virulence for the species, will hardly produce a focus at all, or if such is formed it will soon be encapsulated or absorbed.

On the part of the body, maturity of tissues, freedom from trauma (including such as is produced by inoculation), normal nutrition, and the absence of any exhausting malady or other toxic influence, constitute factors of safety of first importance.

On the other hand, right here we must remember that whatever balance or adjustment may take place *after* tubercle bacilli have established a lodging place in the tissues, no *specific* natural defenses existed so far as we know when they entered. The bacillus undoubtedly has an advantage here, because, given virgin soil and a race of bacilli already adapted to the species, an initial infection takes place with little hindrance from the non-specific defensive powers. The further history of such infections depends in part, at least, upon the amount of specific resistance aroused.

NATURAL IMMUNITY. It has always been easier to define disposition to tuberculosis than immunity. Volumes have been written and an enormous literature has accumulated on the subject of disposition, yet something can conceivably be said for natural or acquired immunity in the qualified sense here used.

Certain species are relatively immune to strains of bacilli occasionally pathogenic for them. The horse and mule, for example, are rarely infected by the bovine bacillus that occasionally may produce disease in them under constant exposure and sufficient dosage. Likewise, swine and sheep are ordinarily resistant to human infection. It does not seem difficult to explain these instances on the ground of non-adaptability of the parasite to races other than those forming its usual habitat.

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[3] Jour. Infect. Dis., 1905, ii, 143.

[4] Cent. f. Bakt. (orig.), xxxviii, 154.

The tubercle bacillus, especially the mammalian type, has, however, shown a rather widespread parasitic power as compared with other pathogenic organisms. It adapts itself also to many kinds of culture media in the laboratory, and there is practical agreement as to the existence of modifications of the two main divisions, human and bovine, Hence when any individuals of a race can be infected we can hardly speak of a natural immunity to all strains of tubercle bacilli.

Some ingenious explanations of the immunity of certain races and species have been propounded. As an example, a plausible theory for the immunity of a certain caterpillar of the bee moth is given by Metalnikoff[5] as the digestive power for wax with which the insect is endowed. Considerable experimental work is adduced by the author to support this idea of the mechanism of protection.

That cellular ferments of lytic character play a prominent part in natural resistance to bacterial infections is a convenient assumption. Otherwise there are temperature conditions, chemical and physiological differences, that can conceivably interfere with the growth of tubercle bacilli in highly resistant animals. We are obliged to leave the question unanswered by any formula capable of demonstration.

So far as man is concerned no race has been discovered that exhibits high natural resistance. The true explanation of any observed differences is quite different, as will be referred to later.

Some observations have been made tending to show a natural resistance in the Zulu natives of Natal, South Africa,[6] also of certain French families.[7] Such instances may be dismissed on the ground that opportunities for infection were limited.

INHERITED AND ACQUIRED IMMUNITY. A consideration of inherited and acquired immunity is more important in its practical results.

Some experimental work has been directed to the solution of the problem as to whether a susceptibility or immunity can be transmitted to offspring of tuberculous animals. No conclusion favorable to immunity to my knowledge has so far been made. The universal observation is that during an active stage of the disease a tuberculous mother has borne weak offspring, which if not, as a rule, tuberculous, often succumb to marasmus or are maldeveloped.

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[5] Zeit. f. Immunität. (orig.), 1914, xxii, 235.

[6] Allen, J. F., Lancet, 1901, clxi, 198.

[7] Dubousquet-Laborderie, La Sem. Méd., 1897, xvii, 307.

If any form of specific resistance is conveyed from mother to young it is too much masked in these cases to be discovered.[8]

The toxic influences on the fetus from maternal disease are added to those affecting the germinal cells before fertilization. Consequently the anti-infectious or antitoxic principles if present are overshadowed.

In point of fact, as stated by Adami,[9] an actual specific immunity acquired by inheritance must be proved through the male parent. "It is essential to immunize the male parent alone, and that through a series of successive generations; and what is to be expected under these conditions is a Mendelian inheritance, certain of the progeny being immune, others not."

From the maternal side we know that substances derived directly from the bacilli can pass through the placenta in one form or another, together with antibodies produced in the mother. The results are disastrous to the young as in the experiments of Carrière,[10] and Maffuci,[11] who injected healthy guinea-pigs with extracts of tubercle bacilli. More than two-thirds of the offspring were either stillborn or died in two weeks. Schenk[12] claims to have demonstrated antibody by means of complement fixation in the offspring of normal and tuberculous guinea-pigs treated with bacillen emulsion. In my own experiments, in association with Dr. A. K. Krause,[13] the inheritance of anaphylactic sensitiveness was demonstrated by injecting pure tuberculoprotein into young guinea-pigs.

These experiments do not, of course, directly relate to the problem of most interest, and that is whether individuals who recover from tuberculosis can transmit any specific resistant quality, be it humoral or cellular. Several authors have assumed the presence of antibodies in the milk of vaccinated cows, which may fairly be considered as recovered animals while their immunity lasts. Von Behring, in 1903, suggested this, and because of the known secretion in the milk of antitoxins for other diseases (tetanus) considered the possibility of a transient passive immunity obtainable in this way. No experiments were published to my knowledge, nor has it been claimed that the calves born of the vaccinated cattle have shown unusual resistance to natural infection.

The only published work that I have found showing either an active or passive resistance in tuberculosis conveyed by milk is that of W. L. Moss,[14] and S. H. Gilliland.[15]

[8] The theory of inherited and acquired "lymphatism" expounded by Bartel comprehends an inherited resistance, though exhibited by a changed form of tuberculosis. Bartel, J., Probleme der Tuberkulosefrage, Deuticke, 1909.

[9] Principles of Pathology, 1910, 2d edition, i, 194.

[10] Arch. d. méd. exp., 1900, xii, 782. [11] Baumgarten's Jahresb., 1902, xxviii, 471.

[12] Folia Serol., 1909, ii, 343.

[13] Studies from Saranac Laboratory, Jour. Med. Res., 1910, xxii, 189.

[14] Transactions National Association for the Study and Prevention of Tuberculosis, 1914, x, 221.

[15] Ibid., p. 228

The former reported on a few calves fed on milk from vaccinated cows. There was a slightly favorable influence. Gilliland mentions a similar experiment with pigs fed on the milk of immunized cows in 1904–5, also suggestive of some protection. Neither experiment was very satisfactorily controlled.

So far no evidence of an experimental nature has shown any form of active immunity to be transmissible. It is quite true, too, that a truly specific disposition, acquired by inheritance, lacks an experimental basis. Here again the bovine race gives a negative to the assertion that tuberculous infection necessarily involves a transmitted weakness or susceptibility. On the contrary, breeding from tuberculin-reacting cows is actually practiced as of eugenic value in preserving the best stocks. The well-known Bang system has been on trial long enough in Denmark to have demonstrated its value, and is, I believe, the approved method of procedure in valuable dairies where tuberculosis is a serious menace.[16]

The observations on cattle here mentioned will not be conclusive that either resistance or susceptibility are stamped on the calves in one generation, but after the lapse of time the future generations should give an answer. They seem to me of great potential value at least in deciding whether the future generations will continue to be affected with the mild form of tuberculosis now prevalent and only discoverable by the tuberculin test.

Then, too, the non-inheritance of tuberculin sensitiveness as such leaves an opportunity for the discovery of some other hereditable quality, specifically adapted to favor or oppose the bacillus. (I shall again refer to the relation of tuberculin reactivity to immunity in connection with the clinical aspect of the problem.)

To make the assertion, finally, that there is no experimental basis for an inherited immunity or disposition does not mean that it is wholly impracticable to reach results of value, though admittedly difficult and wearisome to carry on such work successfully.

We must turn for the present to the biologist, the hygienist, or the statistician, as well as the historian, for further information. Immediately we find opposing views and many facts adduced to support each position. The matter is complex when inquiry is applied to families and races, and not less so in individuals.

Martius[17] took this view, and considers the statistical method inadequate to decide for or against a specific inherited predisposition or immunity. Hueppe[18] believes that both may be inherited, also certain organs show inherited predilection or the opposite for the tubercle bacillus. The latter, at least, has clinical observations to support it.

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[16] A recent contribution by Harlow Brooks (AMER. JOUR. MED. SCI., 1914, cxlviii, 718) testifies that no defects were inherited from a tuberculous cow of unusual milk capacity.

[17] Berlin. klin. Woch., 1901, xxxviii, 814.

[18] Harben Lectures, London, 1903.

Turban[19] showed what he considered an inherited *locus minoris resistentiæ* in the large proportion of pulmonary cases where the morbid process began in the corresponding lung in parents and children. I was able to corroborate this observation in sixty-three families.[20]

I can only mention here some more recent noteworthy works on the subject of heredity in tuberculosis.

Cornet,[21] as is well known, has always scouted any belief in disposition.

Schlüter,[22] in a monograph of considerable size and value, concludes that there is no well-defined specific disposition.

Boeg[23] in studies on the Faroe Islanders gives no support to hereditary disposition.

Grunberg,[24] in a study of 568 families also found no specific heredity.

On the opposite side stands Karl Pearson,[25] the statistician, who by means of strictly mathematical rules applied to 384 families proves a clearly marked family inheritance of diathesis. It is impliedly a specific inheritance, though this appears an unnecessary assumption to me, considering that physical defects from other causes probably form an equally weak resistance and should be considered in estimating the specific element. Practically I think we must accept his conclusion that tuberculous families carry along more of the factors regarded as predispositions, and comprehended under the vague term "diathesis" than the average non-tuberculous family. Insurance interests must necessarily make their rules on the basis of such methods of study. But for the purpose of this lecture, I have only considered evidences of specific resistance, inherited or acquired, and therefore we can hardly confine the study to family groups and a few generations.

In passing, however, it may be of interest to note that such an eminent clinician as Herman Weber,[26] who believed in the heredity of tuberculosis, accepted insurance risks among the fibrous and so-called gouty tuberculous persons, thus recognizing their staying powers in the wrestle with the bacillus.

Leaving the question of family and individual inheritance for the moment, I will briefly mention the racial question. Reibmayr,[27] in an interesting monograph twenty years ago made a fair argument that a gradual process of immunization was taking place in the white race under civilized conditions. His reasoning was that owing to greater care, more weakly children survived to become tuberculous. The disease was consequently more widely spread,

[19] Zeitsch. f. Tub., i, 30, 123.

[20] Yale Medical Journal, 1902, p. 215.

[21] Die Tuberkulose, 2d Auf., 1907.

[22] Die Anlage zur. Tub., 1905.

[23] Zeitsch. f. Hyg., 1905, xlv, 161.

[24] Inaug. Thesis, Paris, 1912.

[25] Draper's Company Memoirs, 1907, ii; also Coring, Charles, ibid., 1909, v.

[26] Medical Examiner, 1898, p. 122.

[27] Die Ehe Tuberculosis u. Ihre Folgen, Wien, 1894.

but it developed chronicity as a sign of increasing resistance. Uncivilized races by contrast exhibited only acute forms of the disease of short duration. The infection is thus limited in extent. This theory admitted the paradox of a disposition and immunity (only relative, to be sure) in the same individual, and in my opinion has much to support it in clinical observation.

Many reports about tuberculosis in late years establish the fact that uncivilized races and those isolated for centuries from the chance of infection, develop acute forms of the disease when exposed. An excellent review of this subject was recently made by Maurice Fishberg,[28] whose well-known studies on the epidemiology of tuberculosis in the Jewish race have shown a decreasing mortality for many years in spite of their ample opportunities for infection. No doubt other factors—indeed, almost countless reasons other than a specifically acquired resistance—may tend to minimize the important conclusion that past generations of Jews have passed on an increasing resistance.

Enough evidence remains, I think, to accept the principle involved which Fishberg elucidates in his recent article, namely, that "the fatality of tuberculous infection depends on the length of time the ancestors of the affected people have been acquainted with the disease."

This principle is accepted with reference to other diseases, such as syphilis, malaria, and yellow fever, and is a rational inference from the known facts about tuberculosis.

There are, however, such marked exceptions to such a generalization that one must consider large groups rather than individuals. There are also other explanations of the relative mildness of epidemic diseases (as mentioned by Professor Theobald Smith) due to the disappearance or weeding-out process of the weaker individuals and races, both of host and bacillus.

I am more impressed, however, with the variability in resistance shown by man than by that of the bacillus. We may leave the subject of racial immunity, in my judgment, with a feeling of hopefulness that some progress has been made in the history of mankind, however slow, toward a self-protection. In this epoch, at least, the bacillus has not appeared to keep pace as an increasingly dangerous parasite.

ARTIFICIAL IMMUNITY. If the question of inherited predisposition or immunity is so difficult of answer, we yet have evidences of an artificially acquired immunity in the life of the individual. An endless amount of work has been done in laboratories and clinics to demonstrate this. A review of even the most important work would not be appropriate here;[29] it is enough to declare that up to now no satisfactory method of active or passive protection has been discovered which applies to man. Nevertheless, I should like to discuss some of the recent contributions to the subject, and especially the reasons for failure as well as partial success. Finally, the application of the knowledge is of value in interpreting clinical tuberculosis.

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[28] New York Med. Jour., September 12 and 19, 1914.

[29] A most satisfactory review may be found in the Kolle-Wassermann Handbuch, 1913, 2d Auf., Bd. v.

Since the disappointment with the vaccination of bovines and serotherapy for tuberculosis the conviction was borne in upon us that only transient protection could be attained, and this chiefly by a vaccine in which the vital spark was not quenched.

Since the time human bacilli were ruled out for use in vaccinating cattle, owing to the short duration of immunity, and their ability to get into the milk, other races of acid-fast bacilli have been put forward for protective inoculation. The feeble resistance obtained in this way merely confirmed previous experiments with them.[30]

McFadyean,[31] of Edinburgh, has more recently advocated avian bacilli for cattle vaccination because non-infectious for human kind, a doubtful assumption considering the occasional presence of such bacilli in tuberculous patients.

Webb[32] even ventured living human bacilli, trusting to small numbers gradually increased in children to avoid infection. This was found impracticable.

The results also with bacilli killed with very gentle heat[33] or devitalized by soap,[34] glycerin,[35] sugar, etc., have been but slightly encouraging thus far.

Vaccines made from the different elements of tubercle bacilli (von Ruck[36]) or from solutions of their substance (Deycke and Much[37]) have also failed to show any advantages over previous tuberculins used for immunization.

The significance of a living vaccine as compared with all substitutes has at present a close parallel in the now much-discussed *immunity from infection.*

The opinion is justified that mild infections are responsible for the considerable immunity hitherto observed in animals inoculated with weak-virulent living bacilli. These mild infections are closely comparable to those spontaneous ones from which the large proportion of our urban population recover. The results of bovine vaccination further justify the opinion that such protection as is conferred depends on the presence of living bacilli or tuberculous tissue in the animal. This protection gradually wanes or disappears with the absorption of the bacilli or the tuberculous tissue.

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[30] Weber and Titze, Tub. Arb. a. d. Kais. Ges.-Amt., 1907, No. 7; Klimmer, M., Beit. z. Klin. d. Tub., 1910, Bd. xvii; Friedmann, F. F., Berlin. klin. Woch., 1912, xlix, 2214.

[31] Jour. Comp. Pathol. and Therap., 1913, xxvi, 327.

[32] Jour. Med. Research, 1911, xxiv, 1.

[33] Klimmer, M., Beit. z. Klin. d. Tub., 1910, Bd. xvii; Smith, Theobald, loc. cit.

[34] Noguchi, H., Jour. Exper. Med., 1910, p. 235; Zeuner, Cent. f. Bakt. (orig.), 1909, l.

[35] Levy, Blumenthal, and Marxer, Cent. f. Bakt. (orig.), 1906, p. 42; 1908, p. 48.

[36] New York Med. Record, August 31, 1912.

[37] Beit. z. Klin. d. Tub., 1910, xv, 277.

The above statement being granted as based on experimental grounds, we may first observe that a spontaneous vaccination of human beings is in progress owing to wide-spread opportunities for infection. Many slight infections must be effective if we will interpret the healed tubercles in that light when found at autopsy. Unfortunately, neither the virulence nor the dose is controlled; hence progressive infections will occur in a considerable proportion of people. If both factors were under control and repetitions of mild infections obtainable at proper intervals it is imaginable that much good would result. Since we cannot assure a stability of virulence for inoculated bacilli, such a dream is far from realization. But we may again inquire, Why is the living bacillus necessary? Cannot the dead bacillus persist a long time in the body and produce tubercles (as we know to be true)? If tuberculous tissue is needed why not use dead bacilli?

The answer is difficult, but it is not likely that the dead bacilli persist long (except when shut off in the form of encapsulated nodules where large clumps may lodge). The tissue changes are also probably less pronounced and certainly more transient. I will also venture the theory that ferments in the living bacilli play a part. Until recently the presence of any function of ferment nature in the tubercle bacillus failed of demonstration. Through the studies of Wells and Corper[38] and those recently published of Kendall[39] and his associates, the presence of a lipase or fat-splitting ferment in the bacillus appears certain. Reciprocal and antagonistic ferment activity on the part of the bacillus and tissues is doubtless a better means of producing an immune reaction than when the ferment action is one-sided.

The studies of Opie[40] in this country, and later those of Manwaring,[41] support the belief that cell ferments combat the tubercle bacilli. Furthermore, the antibodies such as specific lysins are not readily demonstrable in the blood, yet their presence both in the leukocytes and fixed cells cannot be questioned. During a short period following inoculation the blood may contain some specific lysin, though it has not been fully recognized *in vitro*.

Roemer[42] was able to protect two sheep with the serum of another inoculated sheep; later this transferred immunity failed, probably because no serum lysin was left in the vaccinated sheep (some months after inoculation).

The "partial" serum antibody theories of Much[43] and others, while plausible in theory, seem to lack well-controlled experimental demonstration. In truth, no serum antibody[44] in tuberculosis has been definitely associated with immunity; in all experiments the cellular influences appear predominant.

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[38] Jour. Infect. Dis., Chicago, 1912, xi, 388.

[39] Ibid., 1914, xv, 443–471.

[40] Jour. Exper. Med., 1908, x, 419.

[41] Ibid., 1912, xv, 1; 1913, xvii, 1.

[42] Deutsch. med. Woch., 1914, xl, 533.

[43] Ibid., xl, 554.

A most interesting confirmation of this veiw was obtained by Manwaring and Bronfenbrenner,[45] who demonstrated lytic properties in the fixed peritoneal cells of animals. On the other hand, with the serum of vaccinated horses, Ruppel[46] obtained evidence of protective substance of antitoxic nature.

HYPERSENSITIVENESS OR ALLERGY. There is another phenomenon intimately associated with immunity from tuberculous infection with which much speculation and many experiments have been made. This is the hypersensitiveness to tuberculin and especially to reinoculated tubercle bacilli, to which the term "allergy" was given by von Pirquet. It appears to be an important protective mechanism and probably a specific ferment action called forth from the leukocytes and fixed tissue cells by the presence of the invading bacillus or its derived substance.

The similarity and difference between the tuberculin reaction and the tissue reactions following inoculation are being much discussed at the present time; also the analogy to the anaphylactic reactions.

Reviewing the work on the artificial immunization of animals and the attempts to transfer anaphylaxis in tuberculosis, I think we can conclude that the mechanism is the same for all these phenomena. The differences in the manifestation of the reactions are chiefly explained by the presence of focal deposits of tubercle bacilli which can be regarded for comparison in the light of solid particles of foreign protein peculiarly difficult for digestion by the cellular ferments.

It is difficult to understand the cutaneous reactions, and most authors do not consider them anaphylactic manifestations. Unlike the majority of the latter, the skin sensitiveness as well as that of other tissues in a tuberculous animal is dependent upon the presence of tuberculous tissue or tubercle bacilli. Remove the bacilli or the tubercles and one finds that this form of sensitiveness disappears, and with it apparently all specific immunity to the disease is soon lost. The same thing happens when tubercles become thoroughly fibrous or calcified. In the changed reactivity, or the allergic inflammation, therefore, we have the essential features of the relative immunity of whatever grade, acquired in tuberculosis.

It is plain from these facts that a special form of sensitization is produced in tuberculosis by the cellular activities about the bacilli which radiates gradually to distant tissues not necessarily touched by the bacilli as such. Dead bacilli will act temporarily in this way, but pulverized preparations and extracts appear too fleeting in their effects to arouse it. They do nevertheless cause a true anaphylactic sensitiveness without skin manifestations, but unaccompanied by any recognizable immunity. The inflammatory reaction following inoculations of immune animals is the prominent feature, and is conspicuously absent in the others. Hence, we are justly entitled to the opinion that the cell accumulations about the bacilli are performing the duty of dissolving them or restricting their growth. The lymphocytes and endothelial cells have thus received much attention in connection with the tubercle bacillus inasmuch as they show lipolytic activity. The former are especially the reacting cells about the actively spreading foci of disease. Bartel[47] was one of the first to recognize the import of the lymphocyte reaction, and many facts have since tended to confirm it. (Opie,[48] Manwaring,[49] Kling,[50] Bergel,[51] Webb.[52])

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[44] The "anticutines" of Loewenstein and Rappoport (Deutsch. med. Woch., 1904), and the hypothetical antitoxins of Sahli (Tuberculin Treatment, 1912) are too uncertain for demonstration, if indeed such exist.

[45] Jour. Exper. Med., 1913, xviii, 601.

[46] Zeits. f. Immunität. (orig.), vi, 344.

No less important are the endothelial cells in connection with the fixation and absorption of the bacilli as histological studies show, by vital staining methods.

Some recent contributions are noteworthy. Lewis[53] found by the removal of spleen in white mice that a considerable increase of resistance was created to bovine bacilli. A rapid increase of lymphocytes following the removal of the spleen, due to hypertrophy of lymphoid tissue, is a possible explanation. On the other hand, Murphy and Ellis[54] of this city have exposed white mice to Roentgen radiation to destroy their lymphoid tissue and cells with the result that a tuberculous septicemia could be produced as compared with focal disease in control animals.

Much more may be said in relation to cell reactions and hypersensitiveness as a measure of resistance as well as the participation of humoral antibodies or ferments in the reactions.

These may be mentioned in connection with clinical observations.

CLINICAL EVIDENCES OF IMMUNITY. We will now direct attention to a somewhat modern, possibly to some a novel, interpretation of tuberculosis in the symptomatology of the patient.

If our knowledge by experimental methods and observations is to be of value, we should expect to find signs of specific resistance under natural conditions of infection. This term "immunity" is seemingly too strong when used in describing such signs, but when we can discern that life is possibly conserved, and surely prolonged, by the defensive functions, it may not be amiss to employ that word.

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[47] Cent. f. Bakt. (orig.), xl, 48.

[48] Jour. Exper. Med., 1914, xx.

[49] Loc. cit.

[50] Zeits. f. Immun., 1910, vii, 1.

[51] Zeits. f. Tub., 1914, Bd. xxii, 343.

[52] Transactions of the National Association for the Study and Prevention of Tuberculosis, 1910, Sixth Annual Report).

[53] Jour. Exp. Med., 1914, xix, 187.

[54] Ibid., xx, 397.

Tuberculosis from the standpoint of the immunologist is possibly the best illustration of auto-immunity to an infectious agent. From this position we may divide tuberculous infections into four classes:

1. Those which recover without spreading or metastasis of the bacilli.
2. Those which continue to spread acutely, unresisted.
3. Those which progress in a slow chronic form.
4. Those which intermittently progress, becoming arrested in the intervals.

Each form may pass into another in all possible variations.

The types of each are recognized by symptoms except the first. This may only reveal itself by the various tuberculin tests or at postmortem.

It is most important from the point of view above taken, *i. e.*, from that of immunology, that the white race, at least, has for many centuries found a way to recover from repeated infections. We know that the chance of recovery increases from the second year of life to puberty in childhood infection,[55] depending on numerous factors, such as frequency of exposure, amount and virulence of the bacilli, intercurrent diseases, trauma, etc.

We also know that the majority of first infections involve the deeper lymphatic glands, not being resisted at the path of entrance. The course of events from this time forth is of exceeding interest from every standpoint.

We can then trace the path of infection thus far with fair certainty whatever the path of entry. But owing to the allergic state now induced, and which is known to be almost universal in ages over fifteen years (in greater or less degree with exposed families), we find it difficult to associate future disease with a new, exogenous infection. This is a problem about which discussion continues, and which is an important hygienic question.

Exposure to danger of massive infection without disease development in some instances can be ascribed to auto-immunity from earlier slight infections. In other instances it appears to be the cause of later pulmonary tuberculosis of the open ulcerated form occasioned by surface infection.

Both experimental and statistical studies have been brought to bear on this problem of reinfection, the first notably by Hamburger[56] and Roemer.[57] Pathological studies have seemed to give rather uncertain results with reference to the question of new exogenous infections. Recently, however, a few cases have been found where the bovine type of bacillus has been isolated from one part of the body, usually a healed gland, and the human type from a fresh lung focus (Rabinowitsch).[58] Orth,[59] therefore, considers that such early bovine infections predispose to later human infections, yet the link is difficult to fit between them. Naturally, the question of changed type or virulence also comes into this problem.

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[55] Hamburger, F., (Wien. med. Woch., 1914, No. 15) considers all infections in infants under one year develop into progressive disease and 50 per cent. of those in the second year. In ages over four years infection is rarely followed by progressive disease. Only 2 per cent. are found between eleven and fourteen years with an active form of tuberculosis.

[56] Beiträge z. Klin. d. Tub., 1910, xiii.

[57] Ibid., xvii, 383.

Since old foci can break down and cause autogenous reinfection, there is reason to doubt the possibility of new exogenous infection in most cases. The acquired resistance to such a subsequent infection in adult life may be feeble after the complete healing of the old infections, which are usually confined to the lymph glands at the lung hilus or in the near vicinity. In those individuals, while the specific changes in reaction to tubercle bacilli seem to have been lost, when measured by a tuberculin test, we know the old allergy is latent, because in animal experiments reinoculations will arouse it even though no tuberculin reaction can be obtained. This is experimentally shown by intravenous inoculations, a rather extreme method, though we have a human parallel to it in the outbreak of an old focus suddenly rupturing into the blood stream, which is not uncommon in clinical experience. It is generally regarded inevitable that progressive miliary tuberculosis must follow this, and yet it is not necessarily true.

No doubt many of these cases occur, but the number of bacilli, their virulence and frequency in the blood stream, may confine the disease to the upper lobes of the lungs, where complete encapsulation may soon follow the acute febrile reaction. This is not usually regarded as a bacillemia, but we may readily consider it as such in the onset.

The commonly observed exacerbations or relapses in the course of tuberculosis follow the well-known "immune period" of two weeks in so many cases, that we may readily compare them to animals who overcome intravenous inoculations after a protective vaccination. In these it has been found that clumps of agglutinated bacilli are likely to lodge in some other organs, normally resistant to the germ (see Roemer[60]). The parallel may be carried yet further, for in the case of man some bacilli are apt to survive and form new sources of danger in other organs, later emerging as open ulcerations or latent in a soil of less resistance, that is, the lung.

Experience with cattle, sheep, and goats has demonstrated this in various ways, yet in cattle, adult pulmonary tuberculosis is regarded as a new infection from without, obtained in adult life for the most part.[61]

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[58] Deutsch. med. Woch., 1913, xxxix, 105.
[59] Berlin. klin. Woch., 1913, l, 429.
[60] Beit. z. Klin. d. Tub., 1910, xvii, 287.
[61] Smith, Theobald, Harvey Lecture, 1906.

The grafting of new exogenous bacilli in the human lung in adult life nevertheless requires especially lowered health or enormous doses of bacilli. Specific resistance may run down to zero and yet the adult tissues seem naturally prepared for ordinary exposure to infection. Therefore, it is difficult to ascribe the immunity to any allergic state. This seems especially true after the lapse of tuberculin allergy due to complete healing of former foci.

Some inquiries have been made to determine the frequency of adult infection from new sources. In Breslau an investigation of sources of infection by Bruck and Steinberg[62] led to the opinion that both autogenous and exogenous infections caused the adult disease. Hillenberg[63] in a thousand tuberculous cases in the city of Leitz agreed with the above-named authors. He thinks it safe to say that those patients who develop the disease after the age of forty-five years, are due to later infection than childhood unless the disease was in the family. The relative infrequency of the disease in married partners he suggests as being due to a continuous process of immunization due to increasing exposure. The proportion of new infections among sanatorium and hospital staffs is so small that we may use the same explanation to account for it.

The facts anyway appear to show that frequent contact with the bacillus can occur without harm in adult life, and this is a comforting thought. This idea may be new to many who have become phthisiophobic, but a little reflection must arouse curiosity as to the vital resisting powers of many persons in constant contact with tuberculous patients!

As already noted, the absence of resistance in non-infected races ("virgin soil") is of some significance. Nor is it confined to uncivilized peoples, as many instances of acute tuberculosis are seen among healthy adults, particularly from rural districts.

I am not aware that the virulence of the bacillus in these cases is unusual, except for the individual involved. This is shown by the many instances of family infection of all grades of severity. In these the age and amount of infection at the time of primary infection are of great importance.

Whatever the immediate exciting cause of metastatic or fresh reinfection, the result is a higher degree of allergy unless miliary or acute pneumonic disease supervenes. We may note the symptoms of such resistance by the fever, stronger cutaneous reaction and hyperemia about the foci, as, *e. g.*, in the larynx. That the disease now continues to progress is not necessarily because of failure of the immunizing mechanism to act. There may be mechanical reasons, such as trauma and overexercise that cause the bacilli to spread, bringing new foci to the lungs, or elsewhere into the system of tuberculous tissue, thereby heightening the allergy until it reaches a maximum point. From this time a paradoxical state may prevail. The hypersensitiveness now causes a chronic poisoning by its constant activity, or rapid exhaustion occurs from the toxemia. On the other hand, we have reason to believe that but for this protective function miliary tuberculosis might occur oftener in a fatal form.

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[62] Zeitsch. f. Hyg., 1912, lxxi, 177.

[63] Zeitsch. f. Hyg., 1914, lxxvii, 101.

In recent years we have learned the fact that tubercle bacilli wash into the blood stream more frequently than was formerly considered possible, unless an acute miliary disease was present. It is highly probable that many such bacilli are weakened and dissolved by lysis without producing lesions—only causing anaphylactic fever. They may even aid in immunization if intermittently received, so that the dose at any given time can be overcome readily. For example, it is alleged that a tuberculin reaction can produce a bacillemia, which seems to me quite probable to a small extent, yet such a violent reaction as would lead assuredly to loosening bacilli from their moorings has been known to promote a rapid healing. It is not unknown to have other causes lead to strong reactions followed by improvement in the course of a progressive tuberculosis. Such stimulations to the immune reactions are obviously dangerous and unsafe when repeated often, and no experience is so disastrous as an "auto-inoculation" pushed too far, whether by natural means or by tuberculin treatment, artificially applied. It is significant, however, that physical and nervous exhaustion are the most dangerous sources of auto-inoculation.

Moreover, we are familiar with the healing of sluggish ulcers as the result of irritants directly applied, and even intercurrent disease causing the absorption and disappearance of tuberculous foci in the skin, glands, and occasionally elsewhere. The method of Bier by producing alternate passive and active hyperemia has much value and a correct rationale in the light of immunology as applied to tuberculosis.

Stimulation of foci in the lungs, however, requires clinical experience and judgment, for a highly vascular moving organ with, as we have seen, a possible selective affinity for cultivating the tubercle bacillus is to be treated cautiously.

There is often a delicate adjustment or balance in tuberculous disease after it has become arrested. Regarded as a problem in maintaining immunity, the tuberculous individual must be taught to patiently await the time when cicatrization can change the highly sensitive foci to fibrous tissue, before danger of relapse is lessened for those who retain the two-edged sword of hypersensitiveness in an active form.

Here we may refer to the strong contrast between a recently active tuberculosis and one of chronic, fibroid type. In the first there is need of strong lytic action to prevent dissemination of the bacilli. In the fibrous form the bacilli may be abundant in the sputum, but so shut off from the blood that little allergy is present. These latter patients are true "carriers" of tuberculosis, but have no longer any symptoms of absorption from the focus, and consequently low capacity for reaction. They recover very slowly, if at all, but bear stimulation of all kinds more safely. I mention these contrasts for their suggestiveness in treatment.

Interesting examples of the healing of a tuberculous focus in one part of the body while an acute outbreak is in progress elsewhere can be mentioned as auto-immunity phenomena. This is occasionally observed in the larynx during a pulmonary exacerbation, and *vice versa*. The influence of pleural effusion in arresting intrapulmonary disease of the opposite lung is another illustration. The laryngeal swellings often diminish without reactive indications. Likewise, pulmonary ulceration may heal in the course of pleurisy, apparently with no increased inflammation. Immune bodies circulating in the blood best account for these cases, but I cannot offer a satisfactory explanation.[64] The use of autoserotherapy from pleural effusions has been considered rational, on the presumption that immune substances are present; but with what experimental proof I am uninformed.

Many other manifestations of auto-immunity could be cited, including all forms of surface ulceration in advanced tuberculosis, also the various cutaneous affections. These can only be grouped as consequences of the life-protecting functions but not happy in effects.

It remains to emphasize some of the points from which I may draw conclusions.

1. There is no natural immunity to tuberculosis in warm-blooded animals to the types of bacilli found in the bovine or human race.

2. There is a considerable variation in resistance in some species probably due to the chemical effect of their secretions or physiological differences in the animals, but chiefly to the fact that the bacillus has not become adapted to long-continued parasitic existence in them.

3. In the human species no natural immunity is found in any race. All uncivilized races long removed from infection are very susceptible, but the white races, especially the European Jews, have acquired a certain degree of immunity by inheritance and almost universal infection. The rapid increase of intercourse between all lands and races facilitates the universal spread of tuberculosis, which is certain to occur through the medium of numerous bacillus "carriers."

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[64] A few cases of completely arrested advanced tuberculosis following artificial pneumothorax with marked purulent pleurisy have suggested anew to me the importance of the cellular reactions in tuberculosis. The pus which contained tubercle bacilli alone, was repeatedly withdrawn and striking improvement in the intrapulmonary disease accompanied the effusion after it became full of leukocytes.

4. The ultimate survival of those who acquire a relative immunity will tend to diminish the severity of the disease, but many generations may be required to accomplish this.

5. The opportunities for infection, now universal in cities, will diminish gradually in civilized lands by lessening the danger from advanced cases, also from bovine sources. For many years, however, the number of "carriers" will increase owing to improved care, longer life, and higher standards of living among the people.

6. The best degree of resistance against tuberculosis that has been attained by experiments on the lower animals involves inoculation of living bacilli. This is of little value because of short duration of the protection and the danger of sequestered bacilli.

7. The natural infection of human beings takes place largely in childhood and increases the resistance to subsequent disease in a large measure. Under improved care of the tuberculous and better hygiene the amount and frequency of severe infections should diminish, while the number of those with slight, relatively harmless infections should relatively increase.

8. Adults withstand exogenous reinfection under extreme exposure, partly on account of slight infections in earlier life and favorable occupations, environment, and nutrition.

9. The specific immunity acquired from natural infection is largely due to cellular reactions of bacteriolytic nature, which take place outside the blood stream for the most part.

10. The interaction between the ferments of the body cells and those of the bacillus, lead to heightened activity of the lytic power, both lipolysis and proteolysis.

11. The tuberculin sensitiveness or "allergy" is the chief indication of specific resistance. In the patient most of the inflammatory symptoms are due to the actively working immunity functions.

12. In the therapy of tuberculosis this principle should be applied:

To avoid interference with Nature's powers of resistance when she is attempting to localize the infection with apparent success.

FEVER IN TUBERCULOSIS.[1]

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The contributions of physiology relating to heat production and heat dissipation, and the factors responsible for the mainten-

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[1] Read before the Saranac Lake Medical Society, Saranac Lake, New York, Dec. 30, 1913.